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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,947	UMEZAWA ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/12/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 2/12/2007 is acknowledged. However, in light of the prior art cited in the 35 USC 112 1st ¶, 35 USC 102(b) and 103(a) rejections below, it is considered that no search and examination burden exists for the pending claims. Hence, all of the Groups set forth in the restriction requirement are rejoined. Claims 1-20 are pending and under examination.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 6, lines 22-23, page 7, lines 4-5 and 13-14. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The attempt to incorporate subject matter into this application by reference to certain websites (e.g. pages 6 and 7, as detailed above) is ineffective because the nature of websites is transitory and their use to incorporate material (either essential or nonessential) into the specification is prohibited (see in particular 37 CFR 1.57(d)). Neither applicants nor the USPTO has any control on the content and availability of the information referred to at the websites above. Furthermore, the websites are non-patent prior art documents (i.e. not a U.S. Patent or published U.S. application).

The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any

outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

The amendment filed 10/7/2004 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the drawing (Fig. 10) submitted 10/7/2004 depicts a protein in the mitochondrial matrix consisting of EGFPc and DnaEc. There is no disclosure of such a protein in the specification, nor a teaching that that it would be expressed in the mitochondrial matrix without a mitochondrial targeting signal.

Applicant is required to cancel the new matter in the reply to this Office Action.

Sequence Rules

Figure 2 contains amino acid and DNA sequences not identified by a SEQ ID number in the figure itself or in the Brief Description of the Drawings. Furthermore, the DNA sequences

do not appear to be in the Sequence Listing. Applicant must provide a substitute computer readable form (CRF) copy of the "Sequence Listing", a substitute paper copy of the "Sequence Listing", as well as an amendment specifically directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

These details are requirements of the Sequence Rules (MPEP 2400 §1.821-1.825) and must be corrected. Any response which does not include compliance with the Sequence Rules will be considered non-responsive.

Drawings

The drawings were received on 7/20/2004 and 10/7/2004. The drawings of 7/20/2004 are accepted, however, the drawing submitted 10/7/2004 is not compliant with 37 CFR 1.121(d). See the attached form PTOL-324.

Claim Objections

Claim 1 is objected to because of the following informalities: "detecting fluorescence signal" in line 10 should be "detecting a fluorescence signal." Appropriate correction is required.

Claim 9 is objected to because of the following informalities: "protein" in line 1 should be "proteins.". Appropriate correction is required.

Claim 16 is objected to because of the following informalities: "the fusion peptide (a)" is recited twice in line 2, which is redundant and confusing. Appropriate correction is required.

Claim 13 is objected to because of the following informalities: "target different organelle" in line 5 should be " targets a different organelle." Appropriate correction is required

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 10, 16, 18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitations "the other half-peptide of the fluorescent protein" and "the other half-peptide of the intein" in lines 7-8. There is insufficient antecedent basis for these limitations in the claim. This rejection affects all dependent claims.

Claim 10 recites the limitation "the recombinant vector (A)" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 10 recites the limitation "the fusion peptide (b)" in line 6. There is insufficient antecedent basis for this limitation in the claim.

Claim 10 recites the limitation "the other half of the fluorescent protein" in line 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 16 recites the limitation " the fusion peptide (b)" in line 6. There is insufficient antecedent basis for this limitation in the claim.

Claim 16 recites the limitation "the other half of the fluorescent protein" in line 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 18 recites the limitation "the fusion peptide (a) or the fusion peptide (a) expressed by the recombinant vector (A)" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 20 recites the limitation " the fusion peptide (a) or the fusion peptide (a) expressed by the recombinant vector (A)" in line 2. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods wherein a fusion peptide (b) (e.g. as recited in claim 1) comprises a test protein, and vectors encoding such fusion peptides, does not reasonably provide enablement for such methods or vectors wherein the test protein is merely bound to the fusion peptide (b), or bound to the vector encoding fusion peptide (b). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8 USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several

factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art and State of the art. The claimed methods (claims 1-4) require that a test protein, which encompasses any arbitrary protein, be bound to a fusion peptide (b). The fusion peptide (b) is recited as comprising a half-peptide of an intein and a half-peptide of a fluorescent protein (see claim 1). The claimed vectors (e.g. claim 8, from which the other vector claims depend) recite that a test protein is "bound thereto." Thus, for the vector claims, it appears the test protein must bind to the recombinant vector itself, or to the fusion peptide (b) encoded by the vector, which comprises the half-peptide domains listed above for the method claims. Given the above, the specification must reasonably teach how to bind any given test protein to one of the domains recited for the fusion peptide (b), and how to bind such a protein to the claimed vectors or the fusion peptide encoded by the vectors.

The art concerning binding any given test protein to either a half-peptide domain from an intein, a half-peptide domain from a fluorescent protein, or to a recombinant DNA vector, is unpredictable. In a review of inteins published in 2001, Xu et al (Methods, 2001) teach the protein splicing function of inteins, but fail to point out a single protein with an affinity for inteins, i.e. no proteins are known to bind to inteins, or domains of inteins. Likewise, Tsien (Ann. Rev. Biochem., 1998) teaches that green fluorescent protein (GFP, the fluorescent protein used by applicants) has become a useful biomarker, however, there are no teachings of GFP having an affinity for any other protein. Whereas it is easy to envision that one of the many known DNA-binding proteins could bind to the recombinant vector, this situation would, upon expression of the fusion peptide (b) (e.g. as recited in claim 8) yield a fusion peptide (b)

consisting of half-peptide domains of an intein and a fluorescent protein, with the test protein still bound to the vector. The instant specification fails to disclose a use for such a fusion peptide (b), or the vector. Finally, using technology highly related to the instant invention, Ozawa et al(a) (Anal. Chem., 2001, cited by applicants), Ozawa et al(b) (Cur. Opin. Chem. Biol., 2001), and Umezawa et al (U.S. Patent 7,166,447) teach the use of fusion peptides comprising test proteins, half-peptides of an intein, and half-peptides of a fluorescent protein. See, for example, Figure 3 of Ozawa et al(b), the vectors in Fig. 4 of Umezawa et al, or Figure 1 of Ozawa et al(a). In each reference above, the test proteins were part of the fusion peptides, i.e. they were part of the same polypeptide chain. None of the references cited above teach how to make and use fusion peptides wherein the test protein is bound to the fusion peptides (or to the vector), as recited in the instant claims.

Thus, the state of the art regarding binding any given test protein to either a half-peptide domain from an intein, a half-peptide domain from a fluorescent protein, or to a recombinant DNA vector (in the context of the instant invention), is poorly developed. The development of such methods and/or efficacious fusion peptides and test proteins would have to be done empirically.

Number of working examples. Applicants have provided no working examples wherein a test protein is bound to the claimed fusion peptide (b). All that is disclosed is that a test protein is a part of the fusion peptide, i.e. the test protein is in the same polypeptide chain as the intein and fluorescent protein half-peptides. See, for example, Fusion peptide (b) of Figure 1 and the vector diagrams of Fig. 4.

Amount of guidance. Applicants provide no direction or guidance regarding how to make or use the claimed invention wherein a test protein is bound to the claimed fusion peptide (b). The specification requires the skilled artisan to practice trial and error experimentation with literally any test protein to determine which (if any) will bind to the fusion peptide (b) as claimed.

Scope of the invention and Nature of the invention. The claims are broad in nature and read on binding any protein to a fusion peptide comprising a half-peptide from any intein and a half-peptide from any fluorescent protein. The nature of the invention involves the unpredictable art of binding any given test protein to either a half-peptide domain from an intein, a half-peptide domain from a fluorescent protein, or to a recombinant DNA vector.

Level of skill in the art. While the level of skill in the art of making and using the claimed fusion peptide (b), wherein the fusion peptide comprises the test protein, is high, the level of skill in the art of binding any test protein to the claimed fusion peptide (b) is low. The unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Double Patenting

Applicant is advised that should claims 5, 6, 7, or 8 be found allowable, claims 9, 15, 17, or 19, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 9, 15, 17, and 19 merely recite probe sets comprising the fusion peptides or recombinant vectors of claims 5, 7, 6, and 8, respectively, with no further limitations on the structure of the fusion peptides or vectors. The only further limitation that is recited in the dependent claims is an intended use, i.e. "for analyzing organelle-localized protein[s]", which does not limit the structure recited in the independent claims. Furthermore, there is no reason the products recited in the independent claims could not be used for the intended use, thus it is considered that the recitation of an intended use in the dependent claims is not further limiting. See MPEP §2111.02 II.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 6, 8, 17, and 19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 6 and 7 of U.S. Patent No. 7,166,447. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are genus claims anticipated by the species claims of the '447 patent. Claim 1 of the '447 patent recites probe sets comprising fusion polypeptides that comprise the N- or C- terminal domains of an intein and an indicator protein, and a test protein. The indicator protein may be green fluorescent protein (claim 2). Also claimed are vectors that express the fusion polypeptides (claims 6 and 7).

Claims 1-5, 7, 9-16, 18, and 20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, and 4-8 of U.S. Patent No. 7,166,447 in view of Ozawa et al (Anal. Chem., 2001, Vol. 73: pp. 2516-2521), Hamilton et al (U.S. Patent 6,780,599, effective filing date 5/12/2000), Simpson et al (EMBO reports, 2000), and Martoglio et al (TICB, 1998).

Claim 1 of the '447 patent recites probe sets comprising fusion polypeptides that comprise the N- or C- terminal domains of an intein and an indicator protein, and a test protein. The indicator protein may be green fluorescent protein (claim 2). Also claimed are vectors that express the fusion polypeptides (claims 6 and 7), which are used in methods of analyzing protein

interaction by transfecting eukaryotic cells with vectors encoding the fusion polypeptides (claims 5 and 8). Thus, the '477 claims recite all the limitations of instant claims 1, 3-5, 7, 9, 11, 12, and 15, except that the inclusion of an organelle targeting peptide in the fusion peptides is not specifically taught. Furthermore, the '477 claims do not recite the use of different fluorescent proteins (i.e. as recited in instant claims 2, 10, 13, 14, 16, 18 and 20).

Ozawa et al teach a method for analyzing protein interactions in eukaryotic cells using a split-luciferase system wherein two fusion peptides each comprise a half-peptide of an intein, a half peptide of luciferase, and one of the test proteins. See the abstract, Figs 1 and 2, and Table 2. Furthermore, Ozawa et al teach that a similar method is known using a split-GFP system (page 2517, first column, first and second full ¶), and that other applications of the method(s) include evaluating organelle-associated proteins (page 2521, end of the second column). Thus, Ozawa et al teaches all the limitations of claims 1, 3-5, 7, 9, 11, 12, and 15, except that an organelle targeting peptide in the fusion peptides is not specifically taught, although it is suggested.

Hamilton et al teach fragments of fluorescent proteins for a protein fragment complementation assay. These assays involve creation of fusion proteins comprising a complementary fragment of a fluorescent protein fused to each of two protein domains. When expressed in a cell (e.g. by transfection with nucleic acids encoding the fusion proteins), if the proteins interact, the fluorescent protein is reformed and becomes fluorescent, indicating that the proteins are interacting. See Fig. 1, and column 5, line 21 to column 6, line 45. Different fluorescent proteins are disclosed, with different fluorescent characteristics, such as blue and red fluorescent proteins (column 9, lines 44 to column 10, line 10), which would allow the analysis

of two or more proteins per cell or assay (column 9, lines 40-43 and lines 60-64). Furthermore, the system can be used with a targeting peptide fused to the fusion proteins in order to localize the fusion proteins to a subcellular compartment (column 16, lines 7-19). Thus, Hamilton et al teach all the limitations of claims 1-5, 7, 9, 10-16, 18, and 20, except for the inclusion of an intein half-peptide in the fusion peptides, and do not specifically teach the use of different targeting peptides, although different targeting peptides are implied.

Simpson et al teach a method of determining the subcellular localization of proteins by fusing proteins having known or unknown localities (e.g. nucleus, mitochondria, ER) to cyan, green, or yellow fluorescent proteins, transfecting vectors encoding the fusion proteins into cells, and visualizing fluorescence. See the abstract, Figs. 1 and 2, and the ¶ bridging pages 288-289. Simpson teaches that targeting sequences for various subcellular structures are well known in the art, see ¶ bridging pages 288-289. Furthermore, Simpson et al teach the desirability of analyzing protein interactions in the context of its location, i.e. the organelle(s) a given protein is expressed in, see the Introduction on page 287.

Martoglio et al teach that signal peptide sequences, i.e. sequences that direct ER or Golgi localization, are well-known and characterized. See the entire document, in particular Figs. 2-4.

The methods, fusion peptides, vectors, and cells of claims 1, 3-5, 7, 9, 11, 12, and 15 are essentially claimed by the '477 patent and disclosed by Ozawa et al with the exception of the organelle targeting peptide. The ordinary skilled artisan, seeking a method to analyze organelle localized proteins or to localize unknown proteins to an organelle, would have been motivated to use an organelle targeting peptide within the fusion peptides of the '477 patent or Ozawa et al

because both Hamilton et al and Simpson et al teach organelle targeting peptides to be a well known and effective means for targeting fluorescent (or potentially fluorescent) fusion peptides to a desired organelle in order to analyze test proteins within the fusion peptides. Martoglio et al and Simpson et al teach that such targeting peptides were well known and characterized. It would have been obvious for the skilled artisan to do this because of the suggestion by Ozawa et al to analyze organelle associated proteins, and the suggestion by Simpson et al that it is desirable to characterize the subcellular localization of unknown proteins. Furthermore, the skilled artisan, upon reading the teachings of Simpson et al, Ozawa et al, and Hamilton et al would understand that in order for two proteins to interact, and thus produce a fluorescent signal in the methods of the '477 patent and Ozawa et al, they must be localized to the same subcellular compartment and thus both fusion peptides must have a targeting signal directing them to the same compartment or organelle.

Furthermore, the methods, fusion peptides, vectors, and cells of claims 2, 10, 13, 14, 16 18, and 20 are essentially claimed by the '477 patent and disclosed by Ozawa et al with the exception of the organelle targeting peptide (as detailed above) and the use of different fluorescent proteins and different organelle targeting peptides. The ordinary skilled artisan, seeking a method to analyze multiple known organelle-localized proteins, or to localize multiple unknown proteins to an organelle, would have been motivated to use different fluorescent proteins and organelle targeting peptides within the fusion peptides of the '477 patent or Ozawa et al because Hamilton et al teaches multiple different fluorescent proteins to be an effective way to analyze more than one test protein per cell or assay, and because Simpson et al teach that using different fluorescent proteins is an effective means to localize proteins to organelles.

Martoglio et al and Simpson et al teach that multiple targeting peptides were well known and characterized, and Simpson et al teaches that in order to analyze multiple different organelle-localized proteins, different organelle targeting sequences are to be used. It would have been obvious for the skilled artisan to do this because of the suggestion by Ozawa et al to analyze organelle associated proteins, and by Simpson et al that it is desirable to characterize the subcellular localization of unknown proteins, any of which may be targeted to one of a number of organelles, each with distinct targeting peptides. Furthermore, the skilled artisan, upon reading the teachings of Simpson et al, Ozawa et al, and Hamilton et al would understand that in order for two proteins to interact, and thus produce a fluorescent signal in the methods of the '477 patent and Ozawa et al, they must be localized to the same subcellular compartment and thus both fusion peptides must have a targeting signal directing them to the same compartment or organelle.

For the 35 USC §102 and §103 rejections below, claims 9, 15, 17, and 19 merely recite probe sets comprising the fusion peptides or recombinant vectors of claims 5, 7, 6, and 8, respectively, with no further limitations on the structure of the fusion peptides or vectors. Therefore, for reasons set forth in the Double Patenting objection above, and in MPEP §2111.02 II, a teaching of claims 5, 6, 7 or 8 is also considered a teaching of claims 9, 15, 17, or 19. Furthermore, regarding the kit claims, the instant specification provides no guidance as to the

interpretation or metes and bounds of the term. Hence, a reasonably broad interpretation of a kit is a localized collection of reagents, or in this case, more than two cells (i.e. claims 12 and 14). Thus, it is considered a teaching of the cells of the claimed invention is a teaching of the kit claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6, 8, 17, and 19 rejected under 35 U.S.C. 102(b) as being anticipated by Umezawa et al (WO 02/08766, 1/31/2002). Umezawa et al is a WIPO publication in the Japanese language of PCT/JP00/09348, which issued as U.S. Patent 7,166,447, which was based on a translation of the International Application into English (see transmittal papers and PTO-903 in 10/089,040, the corresponding 371 application for PCT/JP00/09348). Thus, the '447 patent is considered an English language equivalent of the WO 02/08766 publication. The '447 patent will be referenced hereafter.

Umezawa et al teach probes, i.e. fusion peptides, comprising half peptides of an intein and a fluorescent protein, and a test protein. See column 2, line 50 to column 3, line 24, and the vectors encoding such fusion peptides in Fig. 4.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7, 9-16, 18, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Umezawa et al (WO 02/08766, 1/31/2002) as applied to claims 6, 8, 17, and 19 above, and further in view of Ozawa et al (Anal. Chem., 2001, Vol. 73: pp. 2516-2521), Hamilton et al (U.S. Patent 6,780,599, effective filing date 5/12/2000), Simpson et al (EMBO reports, 2000), and Martoglio et al (TICB, 1998).

The teachings of Umezawa et al (the '447 patent is used as an English language equivalent of Umezawa et al for reasons set forth above) are as above and applied as before. In addition, Umezawa teaches methods of analyzing protein interaction by transfecting eukaryotic cells with vectors encoding fusion peptides comprising half-peptides of a fluorescent protein, half-peptides of an intein, and test proteins. See the vectors of Fig. 4, column 2, line 43 to

column 4, line 3, Examples 5 - 7. Thus, Umezawa et al teach all the limitations of claims 1, 3-5, 7, 9, 11, 12, and 15, except that the inclusion of an organelle targeting peptide in the fusion peptides is not specifically taught. However, no particular limitations are placed on the source of test proteins (see, for example, column 4, lines 54-56). Furthermore, although fluorescent proteins are disclosed in general, Umezawa et al do not specifically teach the use of different fluorescent proteins (i.e. as recited in claims 2, 10, 13, 14, 16, 18 and 20).

Ozawa et al teach a method for analyzing protein interactions in eukaryotic cells using a split-luciferase system wherein two fusion peptides each comprise a half-peptide of an intein, a half peptide of luciferase, and one of the test proteins. See the abstract, Figs 1 and 2, and Table 2. Furthermore, Ozawa et al teach that a similar method is known using a split-GFP system (page 2517, first column, first and second full ¶), and that other applications of the method(s) include evaluating organelle-associated proteins (page 2521, end of the second column). Thus, Ozawa et al teaches all the limitations of claims 1, 3-5, 7, 9, 11, 12, and 15, except that an organelle targeting peptide in the fusion peptides is not specifically taught, although it is suggested.

Hamilton et al teach fragments of fluorescent proteins for a protein fragment complementation assay. These assays involve creation of fusion proteins comprising a complementary fragment of a fluorescent protein fused to each of two protein domains. When expressed in a cell (e.g. by transfection with nucleic acids encoding the fusion proteins), if the proteins interact, the fluorescent protein is reformed and becomes fluorescent, indicating that the proteins are interacting. See Fig. 1, column 5, line 21 to column 6, line 45. Different fluorescent proteins are disclosed, with different fluorescent characteristics, such as blue and red fluorescent

proteins (column 9, lines 44 to column 10, line 10), which would allow the analysis of two or more proteins per cell or organism (column 9, lines 40-43 and lines 60-64). Furthermore, the system can be used with a targeting peptide fused to the fusion proteins in order to localize the fusion proteins to a subcellular compartment (column 16, lines 7-19). Thus, Hamilton et al teach all the limitations of claims 1-5, 7, 9, 10-16, 18, and 20, except for the inclusion of an intein half-peptide in the fusion peptides, and do not specifically teach the use of different targeting peptides, although different targeting peptides are implied.

Simpson et al teach a method of determining the subcellular localization of proteins by fusing proteins having known or unknown localities (e.g. nucleus, mitochondria, ER) to cyan, green, or yellow fluorescent proteins, transfecting vectors encoding the fusion proteins into cells, and visualizing fluorescence. See the abstract, Figs. 1 and 2, and the ¶ bridging pages 288-289. Simpson teaches that targeting sequences for various subcellular structures are well known in the art, see ¶ bridging pages 288-289. Furthermore, Simpson et al teach the desirability of analyzing protein interactions in the context of its location, i.e. the organelle(s) a given protein is expressed in, see the Introduction on page 287.

Martoglio et al teach that signal peptide sequences, i.e. sequences that direct ER or Golgi localization, are well-known and characterized. See the entire document, in particular Figs. 2-4.

The methods, fusion peptides, vectors, and cells of claims 1, 3-5, 7, 9, 11, 12, and 15 are essentially disclosed by both Umezawa et al and Ozawa et al with the exception of the organelle targeting peptide. The ordinary skilled artisan, seeking a method to analyze organelle localized proteins or to localize unknown proteins to an organelle, would have been motivated to use an

organelle targeting peptide within the fusion peptides of Umezawa et al or Ozawa et al because both Hamilton et al and Simpson et al teach organelle targeting peptides to be a well known and effective means for targeting fluorescent (or potentially fluorescent) fusion peptides to a desired organelle in order to analyze test proteins within the fusion peptides. Martoglio et al and Simpson et al teach that such targeting peptides were well known and characterized. It would have been obvious for the skilled artisan to do this because of the suggestion by Ozawa et al to analyze organelle associated proteins, and by Simpson et al that it is desirable to characterize the subcellular localization of unknown proteins. Furthermore, the skilled artisan, upon reading the teachings of Simpson et al, Ozawa et al, and Hamilton et al would understand that in order for two proteins to interact, and thus produce a fluorescent signal in the methods of Umezawa et al and Ozawa et al, they must be localized to the same subcellular compartment and thus both fusion peptides must have a targeting signal directing them to the same compartment or organelle.

Furthermore, the methods, fusion peptides, vectors, and cells of claims 2, 10, 13, 14, 16 18, and 20 are essentially disclosed by both Umezawa et al and Ozawa et al with the exception of the organelle targeting peptide (as detailed above) and the use of different fluorescent proteins and different organelle targeting peptides. The ordinary skilled artisan, seeking a method to analyze multiple known organelle-localized proteins, or to localize multiple unknown proteins to an organelle, would have been motivated to use different fluorescent proteins and organelle targeting peptides within the fusion peptides of Umezawa et al or Ozawa et al because Hamilton et al teaches multiple different fluorescent proteins to be an effective way to analyze more than one test protein per cell or assay, and because Simpson et al teach that using different fluorescent

proteins is an effective means to localize proteins to organelles. Martoglio et al and Simpson et al teach that multiple targeting peptides were well known and characterized, and Simpson et al teaches that in order to analyze multiple different organelle-localized proteins, different organelle targeting sequences are to be used. It would have been obvious for the skilled artisan to do this because of the suggestion by Ozawa et al to analyze organelle associated proteins, and the suggestion by Simpson et al that it is desirable to characterize the subcellular localization of unknown proteins, any of which may be targeted to one of a number of organelles, each with distinct targeting peptides. Furthermore, the skilled artisan, upon reading the teachings of Simpson et al, Ozawa et al, and Hamilton et al would understand that in order for two proteins to interact, and thus produce a fluorescent signal in the methods of Umezawa et al and Ozawa et al, they must be localized to the same subcellular compartment and thus both fusion peptides must have a targeting signal directing them to the same compartment or organelle.

Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicant's invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633

Notice of Non-Compliant Amendment (37 CFR 1.121)	Application No. 10/501,947	Applicant(s) UMEZAWA ET AL.	
	Examiner Michael D. Burkhart	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

The amendment document filed on *10/7/2004* is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121 or 1.4. In order for the amendment document to be compliant, correction of the following item(s) is required.

THE FOLLOWING MARKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☐ 1. Amendments to the specification:
  - ☐ A. Amended paragraph(s) do not include markings.
  - ☐ B. New paragraph(s) should not be underlined.
  - ☐ C. Other _____.
- ☐ 2. Abstract:
  - ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
  - ☐ B. Other _____.
- ☒ 3. Amendments to the drawings:
  - ☒ A. The drawings are not properly identified in the top margin as "Replacement Sheet," "New Sheet," or "Annotated Sheet" as required by 37 CFR 1.121(d).
  - ☐ B. The practice of submitting proposed drawing correction has been eliminated. Replacement drawings showing amended figures, without markings, in compliance with 37 CFR 1.84 are required.
  - ☐ C. Other _____.
- ☐ 4. Amendments to the claims:
  - ☐ A. A complete listing of all of the claims is not present.
  - ☐ B. The listing of claims does not include the text of all pending claims (including withdrawn claims)
  - ☐ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified. Note: the status of every claim must be indicated after its claim number by using one of the following status identifiers: (Original), (Currently amended), (Canceled), (Previously presented), (New), (Not entered), (Withdrawn) and (Withdrawn-currently amended).
  - ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
  - ☐ E. Other: _____.
- ☐ 5. Other (e.g., the amendment is unsigned or not signed in accordance with 37 CFR 1.4):

_____

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP § 714.

TIME PERIODS FOR FILING A REPLY TO THIS NOTICE:

1. Applicant is given **no new time period** if the non-compliant amendment is an after-final amendment or an amendment filed after allowance. If applicant wishes to resubmit the non-compliant after-final amendment with corrections, the **entire corrected amendment** must be resubmitted.

2. Applicant is given **one month**, or thirty (30) days, whichever is longer, from the mail date of this notice to supply the correction, if the non-compliant amendment is one of the following: a preliminary amendment, a non-final amendment (including a submission for a request for continued examination (RCE) under 37 CFR 1.114), a supplemental amendment filed within a suspension period under 37 CFR 1.103(a) or (c), and an amendment filed in response to a *Quayle* action. If any of above boxes 1. to 4. are checked, the correction required is only the **corrected section** of the non-compliant amendment in compliance with 37 CFR 1.121.

   Extensions of time are available under 37 CFR 1.136(a) only if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action.

   Failure to timely respond to this notice will result in:
   Abandonment of the application if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action; or
   Non-entry of the amendment if the non-compliant amendment is a preliminary amendment or supplemental amendment.

_____ _____

Legal Instruments Examiner (LIE), if applicable Telephone No.